melanoma skin cancer.

DR. LAWRENCE: I will ask Dr. Forbes to come up, and while he comes up I'll answer your first question.

We obviously, in this program that we've presented today, have only followed patients in our presentation to the agency up to 12 months, and in fact, we point that out in our particular recommendations, that these studies have only been conducted up to 12 months.

Clearly, as the drug is brought on the market, we would certainly want to continue to work with the agency on longer term information regarding patients utilizing this drug. I certainly acknowledge that.

And I'll ask Dr. Forbes to answer your second question.

DR. FORBES: And I'll try to do so without too much perambulation here, but let me, if I may, simply point out that the test, as I think most of you know well, the test that is done for photocarcinogenesis is mechanism insensitive. It says

does this drug influence photocarcinogenesis by any means, and does not separate out some of the kinds of issues that Dr. Stern raised.

Now, let me speak to what we do and do not know about photocarcinogenesis, experimental photocarcinogenesis, and the immune responses. We do know that systemic immunosuppression can lead to substantial enhancement of photocarcinogenesis. We've known that for 35 year or so based on mouse studies on antilymphocyte serum and azathioprine, which as systemic immunosuppressive agents significantly enhance photocarcinogenesis. What we don't have as clear a handle on is topical immunosuppression, and where we have treatment modalities that do suppress topical -- the cutaneous immunosuppression situation, such as ultraviolet radiation or nitrogen mustard, both of these are highly carcinogenic in hairless mice, and very much complicate the issue in terms of trying to separate out that issue.

One chemical that we had hoped might help with this issue is uricanic acid, which as we know does suppress some aspects of cutaneous immunology,

but at most the effects that we saw from uricanic acid have been published by others in the literature are equivocal.

That is, if there is any enhancement, it is small in this hairless mouse model so that we do not know clearly that suppressing the cutaneous immune system has anything like the effect that suppressing systemic immunology has on photocarcinogenesis.

Now, to get to the question of mechanistic studies, we can certainly look forward to the possibility of good, basic science studies that will tell us more than we know today about a lot of issues, including immunology and cutaneous immunology. If I had to stand here and make a case and my job depended on selling you on the idea that these had immediate clinical benefit, that is, that they would tell us a great deal about risk analysis and the possibility for doing risk analyses, I'd probably lose my job.

So I can't really convince you that these are of immediate clinical relevance, but I can tell you that there are some things from which we can develop better basic science.

We could, for example, separate temporally the UV aspect from immunosuppression. We could irradiate for, let's say, 12 weeks enough to do a great deal of mutagenic effect in the epidermis, separated by several weeks from changes then that we could induce either systemically or topically in the immune system.

So I think there's no question that scientifically we can separate out some of those effects and in the future at some point have a better handle on what the mechanisms are along those lines.

I think somewhat beyond that, we can look forward to some good transgenic models, either knock-outs or promoters that will also help to separate some of the aspects of the cutaneous immune system and give us a lot more solid science than we have today.

Thank you.

ACTING CHAIRMAN STERN: Thank you, John Forbes.

Why don't we have one last question? We're already way behind time.

DR. SIMMONS-O'BRIEN: I actually have

several questions. So hopefully they won't take long to answer.

I'd like to thank you for a succinct presentation.

I wanted to know were any of the enrollees -- were they biopsied prior to enrolling into these studies, children and adults?

DR. LAWRENCE: We did not require biopsy diagnosis. This was based on a clinical diagnosis. I know for a fact that some patients had been biopsied previously, but we did not require that for enrollment. This was based on the clinical --

DR. SIMMONS-O'BRIEN: Okay. My next question is for the individual who developed the CTCL, and it states that seven-year history of chronic eczematous dermatitis. I wanted to know how was the diagnosis of CTCL made in that individual. Was he a Stage 3B by the time of presentation?

DR. LAWRENCE: The diagnosis was made by biopsy, and --

DR. SIMMONS-O'BRIEN: But what led to that biopsy? Did he have adenopathy or --

DR. LAWRENCE: Yes, he had developed concurrent lymphadenopathy, as well as the lesions that were not responding to therapy. Actually he had tried both with steroids and also with tacrolimus without improvement in the cutaneous symptomatology, and I think that, plus the lymphadenopathy, did trigger.

And I'd like Dr. Joyce Rico, who is one of our dermatologists, who has a better familiarity with the case perhaps.

DR. RICO: The patient, as Dr. Lawrence presented, had lymphadenopathy, had failed to respond to therapy, had a biopsy that was consistent with early mycosis fungoides. His immuno studies were, however, negative, but he was subsequently discontinued from the drug, treated with nitrogen mustard, and did well.

So we suspect that he was a very, very early patch stage 1B.

DR. LAWRENCE: Thank you, Dr. Rico.

DR. SIMMONS-O'BRIEN: My concern is that there are or I have had lots of patients who have been

refractoried to treatment who have been called atopic, and they are head to toe chronic eczematous dermatitis, and a number of them have had mycosis fungoides. So that's why I was interested in terms of knowing exactly what the patient's diagnoses are when you have that particular individual with longstanding history or even short, acute history and total body eczematous disease.

My next question was were there any correlations with blood levels and assessment or were there any assessments, concomitant assessments of white blood cell counts in looking at differentials. Any type of lymphopenia when the blood levels were also assayed for the tacrolimus?

DR. FITZSIMMONS: We evaluated the relationship between blood levels and the occurrence of adverse events and found no relationship between leukopenia and the blood levels that were measured.

DR. SIMMONS-O'BRIEN: Okay, and then my final question was when the patients were enrolled, were they advised to minimize their exposure to sunlight? And how was that monitored and reinforced?

DR. LAWRENCE: They were definitely at the time of enrollment -- were advised to avoid unprotected exposure to natural or artificial sunlight, including and we did encourage and permit the use of sunscreens during the course of the study.

As far as the enforcement, it was asked to be reinforced at each study visit, which as you know were weekly and then every three weeks after that through the 12-week study, as well as the quarterly visits in the long-term study.

I think that is really probably all that we were able to do, which was to ask the sites to reinforce that, and we did certainly strongly encourage patients to practice safe sun.

ACTING CHAIRMAN STERN: A final question from Dr. Bull.

DR. BULL: Okay. I just had a point of clarification. In your efficacy summary, you state that effectiveness is maintained for periods up to one year.

DR. LAWRENCE: Yes.

DR. BULL: Does that include periods of

retreatment or is that sustained -- for ones that had complete improvement, was that sustained up to a year? Was that sustained improvement without further treatment?

DR. LAWRENCE: Let me clarify that. What we meant was in those patients who continued to treat for that period of up to 279 days, they were able to maintain a relative level of improvement. They did not have significant flares or break-through, although isolated and nontreated areas continue to break through.

With regard -- and those were only done in -- that was really a very weak inference from the long-term follow-up of the study patients that were up for to a year where we looked at the easy scores over time, and then we saw them drop and then be maintained at a relatively constant level over time.

With regard to your second question, as I think you were asking two things, patients that discontinue treatment do recur. On average, the patients recur anywhere from as short as a week to as long as a month, but we do see recurrence with these

patients.

So once they stop treatment, they do have recurrence, and the disease does come back, usually not worse than it was before. We are not seeing a lot of rebound phenomenon, but they do recur.

ACTING CHAIRMAN STERN: Henry, the absolute last question.

(Laughter.)

DR. LIM: Hopefully it will be a short one, but this is a follow-up of the point that Rob had brought up before, that many of these patients, they do require treatments in the past or in the future with other modalities, including UBV, as well as PUVA. The light source that had been used in animal studies, I understand in human is going to be quite difficult. In animal studies, it's a broad band light source, and if I calculated correctly, approximately probably it's going to be 90 percent UVA and probably about ten, five to ten percent UVB in there.

And the effect probably, would you be able to say, you know, what is the action spectrum or care to speculate what is the action spectrum, Dr. Forbes,

for the possible photocarcinogenesis that is induced in this particular model specifically with topical tacrolimus?

DR. FORBES: Yes. As to the admission spectrum, Dr. Lim, you're perfectly correct. This is a small percent of UVB, much more UVA, as we find in sunlight, and we believe that in this model the action spectrum for photocarcinogenesis is simply that for untreated skin. That is, we are not looking at photochemistry as a drug here as we would be with 8-methoxy psoralen or some photoactive material. We're looking at the action spectrum of skin, which is largely in the UBV. The UVA adds a very small amount to the effectiveness of the light. The action spectrum as published quite recently in a CIE standard indicates that it has similarities to the erythema action spectrum with small departures here and there.

ACTING CHAIRMAN STERN: Thank you very much.

DR. LAWRENCE: I just wanted to answer two questions you posed in your earlier portion, Dr. Stern, very quickly. One of them is you did raise the

issue about herpes simplex. The frequency of eczema herpeticum in our trials ranged from a low of about less than one percent, about .9 percent in children followed for up to a year and about two to three percent in adults followed for up to two years, to help with that issue.

Secondly, you did raise the issue of immunocompetence locally with patients applying this. Although we did not measure specifically, one surrogate market may be the advent of warts. We have a very, very low incidence of Verruca vulgaris in this study, actually about less than -- I think we had a total of four cases, one in the vehicle, one in the low concentration, and two in the high concentration for a period of a year.

I just wanted to clarify. I was hoping that answered some of your questions.

ACTING CHAIRMAN STERN: Thank you.

Do you have a closing comment as well?

DR. FITZSIMMONS: Just one additional point --

ACTING CHAIRMAN STERN: Sure.

DR. FITZSIMMONS: -- of clarification. In the beginning when you introduced the questions, you raised the issue of the post hoc analysis of the adult showing the difference between .1 and .03 percent concentration. I just wanted to point out that these two studies that Dr. Lawrence described were identically designed, performed at the same time, but at different investigative sites.

So the intention was to always pool the results from those two adult studies. So we believe that the pooling of those results to determine the differences in the efficacy rate between concentrations is a pre-plan not a post hoc analysis.

ACTING CHAIRMAN STERN: I'm sorry. What I meant was the subgroup where you showed that to a large extent, high severity was the group where there was a significant difference.

DR. FITZSIMMONS: That's right.

ACTING CHAIRMAN STERN: It was the subset analysis. I understood that you always planned to pool the adults and the children individually.

DR. FITZSIMMONS: Yeah. So when we did

see the difference, then we further explored where does that difference occur.

ACTING CHAIRMAN STERN: Right, and that's post hoc analysis where I come from.

DR. FITZSIMMONS: Right, and the other point of clarification is that, yes, in the pharmacokinetic study that I described, the 08 study, there was a small body surface area treated. In the clinical trials that Dr. Lawrence described, as you saw, on average 40-some percent body surface area was treated in the pediatrics.

And we also did a pharmacokinetic study in pediatrics and looked at exposure up to 60 percent average BSA, and that data and pharmacokinetics with .1 percent is described in your briefing document.

ACTING CHAIRMAN STERN: I'd like to just make one final comment. I actually think that your presentations were excellent, informative, and very balanced. In terms of the safety data and the analysis of systemic levels, to me it's not so much the mean or the median that's important. What you're really interested in are the outliers where the

effects may be shown because this is going to be used in a very common disease, and I think you emphasized models based on mean and median experience within the group.

The analogy I always use is when I think about how long it takes -- the mean time it takes me to get from work to the airport is 20 minutes, but it's the variance that killed me. It took me an hour and 15 minutes yesterday.

(Laughter.)

ACTING CHAIRMAN STERN: So I'm most interested in -- I think it would be interesting to look at those outliers because they won't be small numbers of people if this agent, in fact, becomes a primary agent for the treatment of a common chronic disease.

DR. FITZSIMMONS: And just quickly to address that, that's why we did the hypothetical worst case, as well as the average. We realize the average is as you described. We want to look at what is the worst case because we know that was the concern, and you saw the safety factors even in that worst case,

the highest blood levels we've seen, the highest AUC. Here's where the safety factors are, and you can see that they're still very large.

Thank you.

ACTING CHAIRMAN STERN: Thank you very much.

Because of my ineptitude as chair, we're of course running behind, but we'll next hear from the FDA presentation. I think what we'll plan to do is keep on going until about 12:30, having either one or two of the FDA presenters, depending on time.

And then what I'd like to do is perhaps take a slightly shorter lunch period, although I understand we have to go next door to have the nearest cafeteria. So we need a little bit longer than we would otherwise because of security and other considerations.

So if we could hear from Dr. Hill, please.

DR. HILL: This presentation will focus primarily on selected nonclinical pharmacology-toxicology data for Protopic, which of course, as everyone knows now, is a tacrolimus ointment for

atopic dermatitis.

Next slide, please.

This shows an outline of the studies that will be focused on, which will include genotoxicity studies conducted for tacrolimus; a photocarcinogenicity study; and a dermal carcinogenicity study conducted for tacrolimus ointment; and then conclusion with an overall summary and the results of these studies.

Next slide.

This slide shows the genotoxicity studies that were conducted for tacrolimus, and they include an Ames mutagenicity test; a mammalian in vitro mutagenesis assay; an in vitro assay of mutagenicity in mammalian cells; and in vivo classigenicity assays performed in mice.

The overall finding from these studies is that there was no genotoxicity signal noted in any of the assay systems.

Next slide.

Photocarcinogenicity study is described on the next few slides, and as you've already heard, the

overall objective for this study is to determine in a hairless mouse model if dermal test article application combined with simulated sunlight exposure can reduce the time to formation of skin papillomas compared to simulated sunlight exposure alone.

Next slide.

There were two major findings noted in this study. The first is that topic administration of the vehicle ointment enhanced photocarcinogenesis. This is defined as shortened the time to skin tumor formation, and its effect was greater in male mice than female mice.

And a second finding was that topical administration of tacrolimus ointment had an additional small influence on skin tumor development beyond the vehicle effect, and once again, this was more prevalent in male mice.

Next slide.

The conclusions from this study is that the sponsor proposed that a caution be included in the label for patients to minimize or avoid exposure to natural or artificial sunlight during the use of .03

percent and .1 percent tacrolimus ointment, and this is a type of precautionary warning that has been in other labels when there was a positive photocarcinogenicity study seen.

Next slide.

The next few slides discuss the dermal carcinogenicity study, and this slide shows the objective of this study, which is to determine in a mouse model if daily dermal test article application can cause the formation of tumors at any organ site after two years of application.

Next slide.

The first significant finding that was noted as there was high levels of mortality exhibited in .3, one, and three percent tacrolimus ointment dose groups. Actually these dose groups had to be deleted from analysis in the study due to high levels of mortality.

The first significant finding was there was a statistically significant elevation in the incidence of pleomorphic lymphoma, which was noted in the .1 percent tacrolimus ointment treated male and

female treated animals compared to vehicle controlled male and female animals.

Next slide.

The second significant finding was that there was a statistically significant elevation in the incidence of undifferentiated lymphoma noted in the .1 tacrolimus ointment treated female animals compared to vehicle control female animals.

Next slide.

On this slide shows in tabular formation the incidence of pleomorphic and undifferentiated lymphoma, and this is just to show that the incidence for the .1 percent male and the .1 percent female at approximately 50 percent was significantly higher than that seen in the vehicle, which ranged from four to 12 percent, and that there was also a significant increase in incidence of undifferentiated lymphoma of 26 percent compared to the vehicle female with two percent.

It's important to note that also there was a relatively high mortality noted in the .1 percent dose group.

Next slide.

The multiples of human systemic exposure levels ranged from nine to 26-fold if the highest mean adult human 24-hour AUC value for the .1 percent tacrolimus ointment is used for the calculation. And on the bottom half of this slide, I show some values that were used to come up with these fold factors.

The first is that the highest mean adult human AUC 24-hour value for the .1 percent tacrolimus ointment is 20.4 nanogram mLs per hour. This is derived from a European study, and it was the highest mean value that was noted, and the details of this study will be discussed further in the next presentation.

The next line shows the value for the mouse study for the 24-hour AUC value of the NOAEL dose, which is identified as the no observed adverse effect level, which in this case is also defined as the dose where no lymphomas were noted.

And this AUC level in the mouse study was 189 nanogram mLs per hour. The next line shows the 24-hour AUC mouse value at a dose where lymphomas were

noted, and this AUC value is 534 nanograms per mL per hour.

So to calculate the range of multiples of systemic exposure levels for the NOAEL does, it would be the 189 divided by 20.4 to give a value of nine, and at the dose where lymphomas were noted, it would be the 534 divided by the 20.4, to give you a value of 26.

This range from nine to 26-fold could provide a certain comfort level on the next slide. However, the multiples of human systemic exposure levels are much less, ranging from three to nine-fold, if the highest obtained adult human 24-hour AUC value for the .1 percent tacrolimus ointment is used for the calculation. Once again, on the bottom half of the slide are the values used for this calculation, and this value, which is the highest adult human 24-hour AUC value for the .1 percent tacrolimus ointment is 61.9 nanogram mL per hour, was once again observed in the European study.

And if you use this value in the final calculations for the NOAEL dose, you come up with the

value of three, and for the dose at which lymphomas were noted, you come up with a value of nine.

So, therefore, your range for the multiples of human systemic exposure levels range from three to ninefold, which presents you with a much less comfortable safety margin.

Next slide, please.

Some conclusions that can be derived from the results of the dermal carcinogenicity study are that the estimates of human systemic exposure data are highly variable and are dependent on the maximum body surface area that is treated in the atopic dermatitis patient.

And at this point in time, it is unclear with the ratio of mouse to human systemic exposure levels would be for pediatric patients since adequate AUC data are not available at this time.

I want to clarify that by adequate AUC data I mean under maximum use conditions.

Next slide, please.

Another conclusion that can be drawn from this study is that the biologic plausibility of

lymphoma formation in local lymph nodes -- what I mean by this is the regional lymph nodes that drain from the site of application -- cannot be ruled out at this time.

However, it is acknowledged that demonstrating this effect could be technically challenging.

Next slide, please.

The first summary slide shows that the results of the photocarcinogenicity study suggests that tacrolimus ointment combined with simulated sunlight exposure shortens the time to skin tumor formation compared to simulated sunlight exposure alone.

Next slide.

And the results from the dermal carc. study summary are on this next slide, and the first point is that lymphomas were noted at the .1 percent tacrolimus ointment dose in the dermal mouse carcinogenicity study. The multiples of human systemic exposure range from three to 26-fold.

The important point is that the multiples

of human systemic exposure calculation is highly variable and is dependent on the systemic exposure level noted in humans.

I'd like to emphasize that the best estimate would be obtained from maximum exposure conditions in pediatric patients.

That concludes my presentation, and the next presentation will be by Dr. Tandon.

DR. TANDON: I'm Veneeta Tandon, the pharmacokinetics reviewer for Protopic. I'll be giving a brief overview of the systemic exposure of topically applied tacrolimus.

Next slide.

The sponsor has conducted pharmacokinetic studies in both adults, as well as pediatrics, in support of their application for Protopic. In adults, I'll be talking about the adult studies first.

In adults the study has been conducted in 12 healthy volunteers using single and multiple topical doses of .03, .1 and .3 percent tacrolimus ointment. Point, oh, three and .1 percent ointment are the two remarketed strains of tacrolimus ointment.

The rest, .3 percent, was an investigational formulation which is three to tenfold higher than the two remarketed formulation.

The systemic exposure of tacrolimus has also been evaluated in 49 adult patients using single and multiple doses of .1 percent tacrolimus ointment in two different studies, and in 35 adult patients with atopic dermatitis using the investigational formulation of .3 percent.

The duration of the studies with the 0.1 percent Protopic was b.i.d. dosing for 13 days. The biggest sampling was done on day one, four, and 14, and b.i.d. dosing for seven days, where the biggest sampling was done on day one and seven.

For the biggest study with seven days' duration, the blood sampling was not (unintelligible) enough to enable calculation of the area under the curve.

The range of the total body surface area treated was between 11 and 60 percent. The number of patients with more than 50 percent body surface area treated was eight.

The systemic exposure of .1 percent Protopic from PICA (phonetic) studies in adult was highly variable, as can be seen on this slide. The AUC zero to 24 ranged from being not calculable to a value of 61.9 nanograms an hour per mL.

The AUC was not calculable because the blood concentrations of tacrolimus were either below the limit of quantitation or were sporadically seen in few sample points.

What I would like to point out here, that when there was more than 50 percent of the total body surface area treated, all blood levels had detectable -- all blood samples had detectable levels of tacrolimus.

The Cmax was less than five nanograms per mL in most patients. However, there were four exceptions to this, four patients who had blood concentrations higher than five nanograms per mL.

In one subject a level of 5.5 nanograms was seen on day 14 at zero hour, and the same patient, a value of 5.3 on day 14 at 24 hours. This person was -- 18 percent of the body surface area was treated

with .1 percent Protopic in this patient.

In a second patient, a value of 9.8 nanograms per mL on day four was observed at zero hour, and 15 nanograms per mL on day 14 at 48 hours, and 29 percent of the body surface area was treated with .1 percent Protopic in this patient.

There were two other patients that had values of 20 nanograms per mL on day one at six hours and at day two, respectively. Body surface area information on this patient was not available. However, this patient was treated with ten grams of ointment as opposed to four and seven grams in the previous two patients.

I would just like to remind you here that the target trough concentrations for transplant patients is between five and 20 nanograms per mL.

The sponsor has also evaluated the blood concentrations of tacrolimus from clinical trials in adults by random sampling. From these clinical trials in adults there were 25 patients that had blood concentrations higher than five nanogram per mL, and these values are shown on the table here.

For patients being treated with .03 percent tacrolimus, there were two patients that had a value of 5.82 and 8.13 at week one, and the tacrolimus blood concentrations in these patients were transient as can be seen. The white blocks there show what their levels were on week three and week 12. They were lower than five nanograms per mL or they were below the limit of quantitation.

The surface percentage, body surface area treated of these patients were 56 and 27 percent, respectively.

In another patient, a value of 5.3 was observed at week three, and the percentage body surface area treated in this patient was 58, and a value of 5.75 was observed in another patient whose body surface area was also 58 percentage.

From Study FJ-111, there were 21 subjects who had blood concentrations between five and 40 nanograms per mL observed between day three and week 26, and the highest observed concentration from the study was 40 nanograms per mL.

And I would like to make a point here that

these concentrations do not necessarily represent the highest achievable blood concentrations of tacrolimus under clinical use conditions because that would depend on the day and the time of sampling.

In addition to the study using the .1 percent tacrolimus ointment, the sponsor had also conducted a study using the investigation formulation of 0.3 percent tacrolimus ointment in adults. I would like to highlight the key findings from the study.

The face and the neck lesions in the adults were more permeable than the lesions on the trunk and the limbs, leading to four and seven times higher exposure of tacrolimus. There was a tendency for lower concentrations of tacrolimus on day eight, and the exception was face and neck regions of treatment. In this case the tacrolimus blood concentrations on day eight were similar to that of day one.

Now, coming to the pediatric PICA studies in the NDA, the systemic exposure was evaluated in 20 pediatric patients using single and multiple doses of .1 percent tacrolimus ointment. The ages of these

patients were between six and 12. No PICA study was conducted in the age range two to five years using the 0.1 percent ointment.

In addition to this study, another study was conducted using the .3 percent ointment in eight pediatric patients between the ages five and 11. There were four patients between the ages five and six, and another four between the age of seven and 11.

Next slide.

The duration of the study using the .1 percent Protopic was b.i.d. dosing for three days. There were three subjects between the age of six and seven, eight subjects between the ages eight and nine, six subjects between the ages ten and 11, and three subjects between the ages 12 and 13.

The range of total body surface area treated was 17 to 83 percentage. The number of patients with more than 50 percent body surface area treated was eight.

The systemic exposure of 0.1 percent Protopic from PICA studies in pediatrics was also highly variable. The AUC zero to 24 ranged from being

not calculable to a value of 27 nanograms R per mL.

The Cmax in the pediatric patient was less than 1.6 nanograms per mL in all the patients.

In addition to the study of the to be marketed strength of Protopic, the sponsor had conducted a study using the investigational formulation of .3 percent tacrolimus ointment in pediatrics. I would again report the key findings from the study.

The younger patients aged between five and six years tended to have higher systemic exposure of tacrolimus compared to the older children ages seven to 11 years.

The older children tended to have higher systemic exposure on day eight as compared to day one.

As I had mentioned earlier, the sponsor has not conducted any PK study in children between the ages two and five. However, this information was obtained from clinical trials where the sponsor had looked at tacrolimus blood concentrations between the ages two and six based on random sampling, and the highest concentrations of tacrolimus observed from

Now, this is an overall comparison of the systemic absorption of topical tacrolimus compared to oral tacrolimus in various patient populations, and the AUC multiples obtained there are reported on the last column.

Comparing the pediatric population, the atopic dermatitis patients had a 32-fold lower area under the curve as compared to the liver transplant patients. Similarly, comparing the adult patients, the atopic dermatitis adult patients had about a 25-fold lower area under the curve compared to the kidney and liver transplant adults.

Next slide.

With this, I will come to the conclusions from the adult and pediatric PK studies. In adults the systemic absorption of tacrolimus after topical application of .1 percent is lower than the exposure generated from oral dosing for transplant rejection.

Pediatrics, an insufficient number of subjects were enrolled in the PK studies to assess the systemic absorption of tacrolimus in pediatric patients below the age of five under maximal use

conditions. Further work in this target population should be considered.

ACTING CHAIRMAN STERN: Thank you very much.

It's 12:25, and it's time for lunch. We will resume promptly at two for the open public meeting because I guess that has to happen on schedule, is my understanding, and then after that we'll have the final presentation from the FDA and questions for all three FDA speakers.

Thank you.

(Whereupon, at 12:26 p.m., the meeting was recessed for lunch, to reconvene at 2:00 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:02 p.m.)

ACTING CHAIRMAN STERN: Good afternoon, everyone. We're about to start the afternoon session of the Dermatology and Ophthalmologic Drugs Advisory Committee meeting number 54.

And this is the time that is reserved for open public comment, and we have a number of speakers. And I'd ask each one to please strictly adhere to a maximum of five minutes. If you go much over that, we'll have to ask you to stop.

Thank you.

MR. HENRIQUEZ: Okay. Just basically some ground rules that we have, and that's with respect to other participants. We ask that in the interest of fairness that you address any current or previous financial involvement with Fujisawa Healthcare.

And our first participant is Susan Toftes.

ACTING CHAIRMAN STERN: Yes.

MS. TOFTES: I have no financial interest with Fujisawa. That's what I need to say here.

My name is Susan Toftes. I'm a registered

nurse working at the Oregon Health Sciences University in Portland, Oregon.

I'm here representing the National Eczema Association for Science and Education, as chair of the board of directors. I also serve on the Dermatology Nurses Association board.

I've worked in a clinical setting with patients who have atopic dermatitis for over 15 years and have been able to see first hand the impact that this disease has on patients and their families.

We recently published a study in the October issue of the Journal of the American Academy of Dermatology showing that in the United States at least seven percent and up to 17 percent of school children have atopic dermatitis. The chronic pruritus causes sleep disruptions impairing patients' ability to concentrate at work and at school. We have many patients in whom this disease has become disabling, affecting virtually every aspect of their life.

Patients use systemic and topical corticosteroids because it's all they have, but it is seldom satisfactory. New treatment options are needed

for this disease because of the long-term side effects of chronic corticosteroids.

Having been involved in clinical trials using Protopic since 1995, I've seen the improvement it has made in the quality of life for patients with this disease, and I'd like to briefly share some words from a letter that a mother of a two year old sent me.

Actually I have two letters, but the first letter I'll read some excerpts from this. The mother's son was two years old when he started using Protopic in an open trial.

"I want to thank the both of you for allowing my son Tucker to be a part of the tacrolimus ointment study. He is doing so much better, 99.9 percent better. Before this miracle medicine -- that's what it's called at our house -- I cried many days and nights praying for relief for my son. I know his misery was indescribable and unimaginable. He would scratch himself to sleep at night, and he and his bed would be covered in blood the next morning. He had socks tied to his hands and feet every night, and sometimes all day. He couldn't wear shorts or

short sleeved shirts. He couldn't play outside like other children when it was hot. It was a constant fight to help him stop scratching, and I had to watch him constantly.

"I can't believe the change in him. He is a totally different child today than he was a year ago. I thank God every day for leading us to you and our miracle medicine. He is happy, active, eats well, sleeps well, and plays well. I cannot explain all the changes that this medicine has made in the lives or our family and especially our son."

And then another little girl. Claire is a five year old. So I'll take the first slide. This is Claire. It's not a terrific lighting in here, but Claire has atopic dermatitis, severe atopic dermatitis actually, and she was diagnosed with AD before the age of one year.

And then the next slide, please.

This is Claire with her twin sister who does not have atopic dermatitis, illustrating the growth impairment that can be due to atopic dermatitis or the chronic steroid use to treat it.

And this is a brief excerpt from the letter her mother sent to us after Claire had been on the open Protopic trial.

"I wonder if you realize what an impact you have had on Claire's life and mine and Pat's as well. We are so grateful to you for Claire's improved condition."

I just urge you as a panel to carefully weigh the information that's been given to you today. Protopic appears to offer a treatment option that is safer, more stable therapy for a serious inflammatory skin disease affecting millions of adults and children.

Thank you.

MR. HENRIQUEZ: Our next speaker is Ben Shaberman.

MR. SHABERMAN: Thank you.

That's Ben Shaberman.

I appreciate you giving me a moment to talk about my experience. I'm a 39 year old person. I've been suffering from eczema for virtually all of my life.

If you want to turn to some of the slides that I have.

(Laughter.)

MR. SHABERMAN: See, it started early.

(Laughter.)

MR. SHABERMAN: I heard you guys refer to the fact that there are a lot of patients who have moderate to severe eczema throughout their entire bodies or over their entire bodies, and that is true for me. It was my ophthalmologist that was the photographer in this case and took this picture and another one about a year ago.

My experience with eczema has been so significant that I wrote an article that was featured in the Washington Post in July called "The Further Adventures of Eczema Boy."

And Eczema Boy, the concept came about because I was defined by my eczema. That was the primary focus that I had on myself, and unfortunately the rest of the world had on me, and as you see these pictures, you can see why.

I've been through every type of treatment,

from herbs to acupuncture, to psychotherapy, to a variety of steroids, antibiotics. I've been what I say juggling steroids and antibiotics my entire life.

I have to say I'm very impressed with the thoroughness of which the Fujisawa people have conducted the study of tacrolimus. I'm very impressed with the advocacy that the FDA is trying to do to advocate for what I believe is the American public and the people that suffer with eczema.

Tacrolimus has been nothing short of a miracle for me. Short of the gash on my head from my car door, I am almost completely clear.

I understand from the discussions as much as I can from the scientific evidence that tacrolimus is not risk free. I don't get the indication that there's this huge risk, but I'll tell you right now I would take a hell of a lot more risk than I see from tacrolimus right now to stop using it.

It's nothing short of a miracle. It has changed my life. If I don't have tacrolimus as a therapy, what do I use? Steroids? Antibiotics? PUVA? Cyclosporin, which I've tried and got very sick

on, or something like interferon gamma, which is highly toxic.

I have no alternative right now, and I beg you to advocate for people like myself who have had severe -- and I say "had" -- severe atopic dermatitis and consider what I've said and what other people are experience with tacrolimus when you make your decision.

I appreciate your time. Thanks.

MR. HENRIQUEZ: Thank you.

Our next speaker is Paula Parsons.

MS. PARSONS: Good afternoon. My name is Paula Parsons, and I'm here on behalf of my son Joseph. He's currently 11 years old. He's in the sixth grade.

He was diagnosed with atopic dermatitis shortly after birth. We have gone through dermatologists, physicians, all who have as of February of this year gave up on us.

He's been through corticosteroids, oral, topical. We've done the herbal baths. We've done the oatmeal. We've done everything.

My son's nickname at school was "Lizard Boy." He has suffered emotionally and physically. He's gone without sleep. He's gone without friends. This drug has changed our lives. It's changed my entire family's life.

He no longer scratches in his sleep. My other son can now sleep because he's not making the scratching noises.

He's got friends at school. In a matter of six weeks, he has developed friends. He even came to me and asked to go school clothes shopping, the first time in his entire life. It has changed our lives.

And he would like to tell you how much it has changed his life.

MR. PARSONS: This medication was -- made me feel a lot better, and in just one week I felt a lot better. It's been something I've been praying for all my life.

MS. PARSONS: Thank you.

MR. HENRIQUEZ: Thank you.

Our next speaker is LaDonna Williams.

MS. WILLIAMS: Good afternoon, and that sure is a hard act to follow.

(Laughter.)

MS. WILLIAMS: I was speaking to him earlier, and I've really enjoyed getting to know him.

My name is LaDonna Williams, and I am the co-chair of the Coalition of Patient Advocates for Skin Disease Research. I am also on the board of the National Eczema Association, and I'm working with and help developing other skin groups that offer patient advocacy.

But today I'm here as a mom. I'm here as a parent of three children, two of which suffer from full body eczema. My daughter is 23 and my son is 15. They have spent their whole life with eczema. They have spent their whole life itching and scratching and oozing and rashing and crusting, and it becomes unbearable.

As many of you who are parents know, when you have an infant or a young child, even toddler maybe, you're not expected to sleep through the night. Well, my son was seven years old before he slept

through the night. The scratching was unbearable for him.

And when they are clear, it's because they're on steroids, oral or topical steroids, and we all know what that can do and what type of side effects that can cause.

So I'm here to plead for my children who are not on these studies and who need a medication that can help him and provide them a little comfort because it doesn't just affect the children in the household or an adult. If you have this disease, it's a disease that affects the whole family.

So I'm here with a positive for this new medication. It's been referred to as a miracle, and as Joey -- when I asked Joseph what he thought of it, if he could sum it up in one word how would he sum it up, and his word was "weird."

So be it weird or be it a miracle, I hope to pray my children will have an opportunity to use it.

Thank you.

DR. HENRIQUEZ: Thank you.

Our last speaker will be Dr. Robert Stern, who will be reading excerpts from a letter from Dr. Elias.

ACTING CHAIRMAN STERN: The members of the committee and the FDA were all sent letters from -- a letter from Dr. Peter Elias, who's a professor of dermatology at UCSF, and at lunch we thought it might be appropriate to put some sections into the public record since he's not here, and I'd like to start with this is, first of all, excerpted, but I'd like to start first of all with his conflict of interest disclaimer.

And it says, "Please note that Dr. Elias is a consultant for cosmetic companies that have developed or are developing emollients as potential alternative safe therapy for atopic dermatitis."

Let me by reading a few paragraphs summarize his letter to us.

"I am among those clinicians eagerly awaiting the addition of topical tacrolimus to the therapeutic armamentarium because it seems clear that this drug will be particularly useful to induce

remissions in severe, recalcitrant atopic dermatitis. Both in severely affected children and adults with AD, tacrolimus appears to produce rapid clearing in the majority of patients.

"However, two recent articles of the Archives of Dermatology and other recent publications elsewhere raise serious concerns that tacrolimus will be prescribed more widely than is appropriate. Thus, it is very important that the labeling for the drug clearly indicate its proper intended use, and that all known and potential risks be clearly communicated."

I'll skip his description of these reports and go on.

"In the first report, the title and study design themselves suggest (a) that tacrolimus is appropriate for the long-term therapy of adult AD; (b) that tacrolimus is appropriate not only for severe AD, but also for moderate disease, i.e., disease which presumably is also responsive to standard therapy; and (c) that tacrolimus is an effective form of maintenance therapy for AD, and that tacrolimus use long term is safe and safer than standard therapy."

And I'll just close with the end of his letter, which says, "How can we be sure that very low levels of tacrolimus percolating in the skin alone won't increase the risks of either T cell lymphoma and/or an increased propensity for skin cancers in locally UVA irradiated immunosuppressed skin?

"Finally, do we know that local immunosuppression does not increase susceptibility to skin colonization by microbial pathogens, such as Staph. aureus?

"In summary, I share the excitement that a new therapeutic dimension brings to our capabilities to help suffering patients. Yet I am alarmed at what appears to be a potentially cavalier and uncritical attitude about the indications and long-term safety of topical tacrolimus. Isn't this current situation reminiscent of the wave of enthusiasm that accompanied the initial release of isotretinoin that also leads to excessive and inappropriate prescribing?

"Sincerely, Peter M. Elias."

I apologize to Fujisawa Healthcare in my pronunciation. As one of you had difficulty with one

of my words, I've always had difficulty with pronouncing the name of your drug.

If there are no other public comments, we'll close this part of the meeting, and Dr. Okun will present -- oh, I'm sorry. Please identify yourself and any potential conflict of interest.

MR. KENNEDY: Good afternoon. My name is Anthony Kennedy. I have no conflicts of interest here.

I'm a 47 year old atopic dermatitis patient who's currently a study patient. I was pretty much over 75 percent of my body, although fortunately I'm like "Eczema Boy." It's didn't affect my face.

Like many other patients, I was unsuccessful in planning an effective treatment until the study drug. The study drug has been effective. I've been using it for about six months, and I hope it gets approved, and I've noticed no ill effects from it.

So thank you.

ACTING CHAIRMAN STERN: Thank you.

Are there any other public comments?

(No response.)

ACTING CHAIRMAN STERN: If not, we'll close this part of the meeting now, and if Dr. Okun could present the final part of the FDA presentation.

DR. OKUN: Good afternoon. It's not customary for FDA speakers to interject personal comments, but I would like to start off by saying how much I was really moved by the testimonials of the public speakers and how much I admire their courage in speaking to us, and I am sure there are many others in this room who feel the same way as I.

Given the most thorough presentation of Drs. Fitzsimmons and Lawrence this morning, with your forbearance I would like to and in the interest of time I would like to avoid repeating some of the information that has already been presented. So some of the slides which we are going to go through, which are essentially repetitions of what you've seen before, we'll just spin through very quickly.

Next slide.

Protopic ointment has been studied in adult and pediatric patients for a variety of time

periods, three weeks, 12 weeks, six months and 12 months, and in a variety of ointment strengths, .03 percent, .1 percent and .3 percent. At present the .03 percent and the .1 percent ointment are being considered for marketing.

Next slide.

With respect to safety, Dr. Lawrence's presentation focused on the five core Phase III studies, and in our review of the entire Protopic safety database, we are going to be focusing on the serious adverse events and adverse events that led to discontinuation from study, and also focus on adverse events consistent with systemic immunosuppression, such as, for example, lymphadenopathy, lymphoma reactivation or primary infection with VZV and HSV.

Next slide.

So we've broken this down both by adult and pediatric patients, looking at the variety of time intervals. Looking among adults treated short term, you can see that serious adverse events and adverse events that led to a discontinuation from study were relatively rare.

Next slide.

And over a three-week treatment period, the reactivation of VZV infections and HSV infections were noted in a relatively small percent of subjects. These patients here were confirmed according to the case records as having zoster rather than primary infections.

The incidence obviously is very low, and in many cases there's no vehicle on here. So we can't really compare it to what the background rate is, but certainly the percentage is very low.

Next slide.

For intermediate term studies of 12 weeks in duration, the percent of patients who experienced adverse events that were sufficient to trigger discontinuation from the studies were somewhat higher than what was seen in the three-week study. Most of these adverse events were local effects, such as burning, stinging, erythema, pruritus.

And interestingly, there's no notable difference in the incidence of adverse events that led to discontinuation in comparing subjects in the .03

percent and the .1 percent arm.

Next slide.

Again, looking in the adults at the 12-week study, the incidence of HSV reactivation was low, but not zero, ranging between two and three percent, and it included some patients who developed Kaposi's varicelliform eruption or eczema herpeticum.

Next slide.

In long-term studies in adults, this slide indicates that, in general, medication was relatively low tolerated with a comparatively small percentage of patients experiencing serious AEs or AEs that led to discontinuation.

Next slide.

Some adult patients in the long-term study did progress to VZV infections. It is unclear, however, from these case reports if these VZV infections, Varicella Zoster Virus infections, were primary infections, zoster, or disseminated zoster. Details in the case reports do not permit us to tease out how they should specifically be classified.

About 67 percent of the patients

Now, in the 12-week study in pediatric age group, all the VZV infections were clearly identified as chicken pox, in other words, primary infections, not zoster, and noteworthy adverse events included several cases of Kaposi's Varicelliform Eruption.

Next slide.

Looking at the one-year studies in pediatric age groups, they've been conducted with three tacrolimus strengths on multiple pediatric age group ranges. So I apologize that this chart is somewhat or this table, rather, is somewhat busy, but the take home message is that the adverse event profile is very similar to what was seen in the one-year study in adults.

Next slide.

Now, let's turn to the one-year study of the .1 percent ointment in pediatric patients. Seventeen patients in this group, which works out to two percent of the population had evidence of Varicella Zoster Virus infection.

According to the case reports, there's one definite case of herpes zoster, seven cases of

definite chicken pox, and the other nine cases, it is not possible to tease out from the descriptions precisely what type of infection they had.

Now, if we assume that none of the other nine had herpes zoster, then one zoster case in the pediatric age group out of about 800 patients is within reasonable expectations for a normal population.

Of course, if more of those, if several of those other nine cases turned out to be zoster, that would be higher than, I think, what would be expected in a normal population group.

Next slide.

Now let's turn to the reports of lymphadenopathy in clinical studies. Now, we're looking at all patients exposed, both adults and children, for a variety of durations and a variety of strengths, all in this one slide.

There's a total of 33 cases have been reported.

Next slide.

Let's talk about the etiology of these

lymphadenopathies. Two case reports bear special mention. One is a 68 year old male who developed a parotid lymphoma. According to our reading, it's uncertain if this lymphoma was a preexisting condition or not.

If I refer to the patient summary of that patient's description, he initially enrolled in the 12-week study in January of '98, and his history and physical exam was apparently unremarkable according to the case report form enrolling him in that study in January.

Completed the study in March, and then he enrolled into a longer term follow-up study in March of '98.

On December of '98, he was seen by an ENT specialist for the pre-auricular mass on the right side, which he reported as being present for about a year, and this was a mass that was described as a 1.5 centimeters, firm, slightly mobile and nonpainful.

And he subsequently underwent surgical removal of the mass. The final surgical path. report was malignant lymphoma, small cleaved cell type with

focal sclerosis.

So, you know, clearly the patient claims based on his summary that he thought it was present for about a year, but we don't have hard, objective data to support that.

Okay. We also have another case of lymphoma, a 59 year old male who, I think, Dr. Lawrence described in detail earlier. Was diagnosed with cutaneous T cell lymphoma during the one-year study.

Turning away from the lymphomas and towards other lymphadenopathies, there were six cases with no clear etiology, four of which result spontaneously during continued treatment. Two patients discontinued therapy with the lymphadenopathy and were lost to follow-up.

Eleven cases it seems pretty clear are related to skin infections. Nine of those cases resolved on antibiotics. Three discontinued therapy, but had resolution with their lymphadenopathy. Twelve other cases were related to upper respiratory infections which resolved on antibiotics, and two

cases were related to tooth infections.

So the majority of the lymphadenopathy cases we feel fairly comfortable in ascribing a clear etiology, but can't necessarily do that for every one of those lymphadenopathy cases that have been recorded in the safety database.

Next slide.

Now, turning to more common adverse events, looking across all three 12-week studies, it's difficult to compare the adverse event rates across vehicle and active treatment arms because, as Dr. Lawrence mentioned this morning, a significant fraction of patients, more than 50 percent of the patients in the vehicle arm, discontinued treatment.

Having said that, the application site adverse events, such as burning, pruritus, erythema, treatment site infection, the rates were higher in patients treated with the .03 percent ointment and the .1 percent ointment than the patients treated with vehicle.

There is no obvious increase in local, common adverse events as concentration increases.

Next slide.

Looking at common adverse events in the one-year studies with the .1 percent ointment, which includes both pediatric and adult studies, 54 percent of the pediatric patients in the one-year study and 78 percent of adult patients in the one-year study reported application site reactions. The majority of these were not severe, and the prevalence of skin burning declined to less than ten percent by week four of the long-term studies.

Next slide.

So in conclusion in a review of the safety database, most patients tolerated the .03 percent or .1 percent ointment concentrations, with ointment use being associated with application site reactions in about 75 percent of patients. Most such reactions were mild and transient.

Tacrolimus, .03 percent and .1 percent ointments had similar adverse event profiles.

Next slide.

The possibility of an increased incidence of herpes zoster, herpes simplex, Kaposi's

Varicelliform Eruption may exist. Two patients developed lymphoma during study conduct.

No inference is being made here with respect to causality.

Six patients developed lymphadenopathy with no obvious etiology.

Next slide.

Now, I'd like to turn to the efficacy database, and it is principally built upon three identically designed, multi-centered, double blind, randomized studies that have been described in great detail earlier this morning. So we can skip to the next slide.

This slide summarizes the characteristics of the study patients who were enrolled, and again, Dr. Lawrence has covered this. So I think we can skip to the next slide.

This describes a few aspects of the study protocol, which again has been described. I'll just add that the prespecified treatment success at week 12, which was complete clearance or greater than or equal to 90 percent improvement, was agreed upon prior

to conduct of the pivotal studies between FDA and Fujisawa.

And while this was the agreed upon primary endpoint in 1996 prior to commencement of these studies, currently we prefer to have an efficacy endpoint where the outcome is not dependent on investigators recalling baseline status from 12 weeks prior to the assessment at end of treatment.

Next slide.

And here's just a tabular presentation of the same data that Dr. Lawrence presented earlier graphically. Clearly for all three studies both treatment arms had markedly superior outcomes compared to the vehicle arm.

Next slide.

In all three studies the .1 percent and 0.3 percent were statistically significantly superior to vehicle. The .1 percent ointment was numerically but not statistically superior to the .03 percent ointment, with the treatment differences of six and 12 percentage points in the 035 and 036 studies, the two adult studies, and a treatment difference of five

percentage points in the 037 studies.

Now, the lack of statistical superiority between the .1 and the .03 percent ointment may be due to at least two factors, one possibility or two possibilities rather. One possibility would be that the two drug concentrations actually have equal efficacy. The other alternative is that the studies have a Type II error, that they might have been under powered to detect a statistically significant difference, of course, the active treatment arms.

Next slide.

And clinical studies may not have been adequately powered to detect statistically significant, clinically relevant differences in treatment effect between .03 percent and .1 percent ointments.

Each individual study, 035, 036, 037, is powered to about .18 to detect a ten percentage point difference, which we would consider a clinically relevant difference, and the power of about .8 to detect an 18 percent point difference, which is quite a marked clinical difference.

Next slide.

Arguing in favor of the notion that the .1 percent ointment is not statistically superior to the .03 percent because of this Type II error is the observation that .1 percent is numerically superior to the .03 percent in numerous population subsets, and as Dr. Stern mentioned earlier, this is obviously -- these are analyses that are being conducted in a post hoc manner, but I think it's instructive to see that, of course, a lot of different population subsets, .1 percent is consistently numerically superior, in males and in females, in Caucasians, in African Americans and Asian Americans, in patients with baseline moderate disease and patients with baseline severe disease, in patients who are older than 65 and who are younger than 65.

Next slide.

Similarly, in looking at the pediatric efficacy database, the .1 percent is numerically superior to the .03 percent in Caucasians, in African Americans, in Asian Americans, also in patients with moderate baseline disease and with severe baseline

disease, in patients aged two to six years old, and in males.

Next slide.

The .03 percent is numerically superior to the .1 percent in two of these population subsets, ages seven to 15 and in females, and I think you can see from the slide that the differences are quite minute.

Next slide.

Looking at some clinically relevant secondary efficacy endpoints, comparing outcomes between the .03 and the .1 percent, in all three studies, all three pivotal studies, the .1 percent ointment was numerically superior to .03 percent with respect to the percent of patients with complete clearing at end of treatment, the reduction in percent body surface area involvement at end of treatment, the percent of patients with greater than or equal to 50 percent improvement at week one.

Looking at the patient's assessment of pruritus, the .1 percent ointment was numerically superior in one study, numerically inferior in

another, and equal in the pediatric study.

Next slide.

So efficacy conclusions are that both tacrolimus concentrations were statistically significantly efficacious over vehicle. The tacrolimus .01 percent ointment was numerically efficacious over the .03 percent ointment with respect to the overall primary efficacy variable. Most clinically relevant population subsets, most clinical relevant secondary efficacy variables.

Next slide.

The clinical studies may have been under powered to detect clinically relevant, statistically significant differences in treatment outcomes between tacrolimus 0.1 percent and 0.3 percent ointments.

Next slide.

Now I'd like to turn to a discussion of the potential risk associated with use of this ointment. Dr. Tandon this morning indicated that tacrolimus blood concentrations are detectable in subjects using tacrolimus ointment for treatment of atopic dermatitis.

So the question turns to: what is the potential risk of systemic immunosuppression induced by percutaneous absorption of tacrolimus? And, more specifically, what is the lowest amount of tacrolimus percutaneous penetration at which clinically relevant systemic immunosuppression occurs?

I think we really need to answer these questions to get a firmer grip on the issue of the potential risk associated with this treatment.

A manifestation of systemic immunosuppression in organ transplant recipients, some of the patients who have been exposed to systemic tacrolimus, is lymphoproliferative disease, which is often associated with aggressive immunosuppression. It's frequently associated with acute or past infection with Epstein-Barr virus and may progress to lymphoma or death.

Next slide.

Lymphoproliferative disease in adults, the prevalence is estimated at about 0.8 percent in transplant patients. The spectrum of disease ranges from polymorphic, polyclonal B cell proliferation to

frank lymphoma. It is most often associated with aggressive immunosuppression and EBV infection.

Treatment includes reduction in immunosuppression, antiviral therapy, debulking of tumor, chemotherapy, and radiotherapy.

Spontaneous regression can occur, but mortality is over 50 percent.

Next slide.

In children, the same disorder. Its incidence is estimated to be from four to eight percent in transplant patients. The three major risk factors are allograft type, EBV infection or reactivation and immunosuppression.

It can affect any organ system and can be diffuse or focal. Abdominal disease is most frequent.

Treatment involves reduction in immunosuppression, treatment with antivirals, and conventional antineoplastic therapy.

Regression after withdrawing immunosuppression ranges from 23 percent to 65 percent. Mortality is lower than in adults, approximately 20 to 50 percent.

Next slide.

It takes a mean time of about 12 months of continuous immunosuppression with oral tacrolimus for patients to develop lymphoproliferative disease, and we have here a comparison with the same time span for cyclosporin and also time span for tacrolimus rescue, where patients are initially treated with cyclosporin A but rescued with high dose tacrolimus secondary to graft rejection.

Next slide.

The trough blood levels of tacrolimus correlate with systemic immunosuppression, and following organ transplant -- I think this has been mentioned earlier -- the goal is generally in the first month post transplant to maintain trough blood levels of about 15 to 15 nanograms per mL, plus transplant months one to three maintain about ten nanograms per mL, and post transplant months three to six, five to ten nanograms per mL. After post transplant month six in selected patients, less than five nanograms per mL may be adequate if graft function is stable, but immunosuppression is highly

variable at that level.

Next slide.

In the pivotal controlled studies for this NDA, blood samples were collected at weeks one, three, and end of treatment in some of the patients to measure tacrolimus blood levels, and it's important to mention that the blood samples were collected at random with respect to time of last tacrolimus application, i.e., these are not trough levels.

Next slide.

And this is a table which shows the distribution of tacrolimus blood concentrations for pediatric patients aged two to six, and for pediatric patients aged seven to 15.

Now, the majority of patients in the two to six year old group never had blood levels above the lower limit of detection. A higher percentage of patients in the tacrolimus 0.1 percent arm did have detectable levels, and those that's here adds up to 9 percent. Their detectable levels, in general, were more likely to be higher than the patients in the tacrolimus .03 percent arm, where only 12 percent of

the patients had levels that were detectable, and in general they trend towards lower concentrations.

In the patient ages seven to 15, the numbers are small, but all of them had no detectable amounts of tacrolimus in their circulation.

Next slide.

Comparable results are seen in blood samples collected in the adult studies with two interesting differences. First of all, here some of the blood samples contain greater than five nanograms per mL, and although the trend in the patients in the .03 percent arm was to have lower blood concentrations, in fact, the two highest concentrations were noted in the patients with the .03 arm. That was an observation of 8.13 nanograms per mL and 5.82 nanograms per mL.

Next slide.

So what accounts for these isolated elevated tacrolimus blood levels? And specifically, why the two highest levels detected in the .03 percent arm even though the trend is for more patients in the .1 percent arm to have levels above the lower limit of

detection?

We don't have a definitive explanation. We have some possible explanations. Isolated patients in the .03 percent arm may absorb more tacrolimus systemically because of less efficacy associated with treatment with that concentration.

There may be another covariate completely unrelated to treatment arm that explains these results.

There may be variability in the tacrolimus assay, and of course, another explanation is just a chance finding.

Next slide.

Let's look at the clinical outcomes of the patients who experienced these blood level spikes, and I think Dr. Tandon presented some of this data earlier. I wanted to show this to show you the correlation between the blood levels and the clinical evaluations contemporaneously.

In study number 035, the patient enrolled by week one had an elevated level and, corresponding to that, had a clinical evaluation showing only slight

improvement. By week three when that patient had reached marked improvement, the blood level had fallen from 5.82 to .5. It was still detectable at end of treatment, level of two, but clearly was lower than at the first week of treatment.

Similarly, the analogous pattern or the similar pattern is seen in the next row, in study number 036. The patient at week one had a very, you know, clearly detectable level of tacrolimus, 8.13 nanograms per mL, and corresponding to that had a clinical evaluation of showing only slight improvement.

Later on in the clinical study when he had experienced moderate improvement, the level fell below the limit of the quantification.

Apparently it's a little different in the third row where here the highest level, 5.3 nanograms per mL, is seen at week three rather than at week one, and this patient was reported as being markedly improved. When he progressed on to being cleared at the end of treatment, his blood tacrolimus concentration had fallen.

Next slide.

Interestingly, in comparing the percentage of patients with moderate improvement or better by week one of these pivotal studies, of course, all three of the pivotal studies, a higher percentage of patients in the 0.1 percent ointment arm had moderate improvement or better by week one compared to patients in the .03 percent arm, which creates the possibility that by improving patients more quickly, it is possible that the 0.1 percent ointment may reduce the percentage of patients who are susceptible to absorbing high levels of tacrolimus early in their treatment course.

Next slide.

Looking at -- this is a very busy graph, and it shows the traces, of course, a one-year study of each individual's tacrolimus blood levels, and what you can see, I think, and the general pattern is that over time in the 52-week study, the concentration does tend to decline.

However, there is marked variability noted throughout the study, and there are some patients even

out to 52 weeks who do have detectable levels of tacrolimus in their blood.

Next slide.

In fact, 60 percent of subjects had persistently elevated above the limit of detection tacrolimus blood concentrations. This percentage of 60 percent refers to subjects who did not have a specimen measuring below the limit of quantification within any of the following time periods: week one, week two, months one, three, six, and 12.

It's important to note in evaluating the significance of this percentage is that not all subjects had measurements within each of these periods. So some of these so-called persistently elevated subjects may have had only a couple of readings each of which was elevated.

Next slide.

Of the 48 subjects who did have six specimens collected across this long-term time period, 54 percent had detectable tacrolimus concentrations in all specimens.

Next slide.

This slide summarizes the potential risk of systemic immunosuppression following topical versus systemic exposure to tacrolimus. The risk associated with systemic tacrolimus is that it is usually lifetime exposure with at least six months of greater than five nanograms per mL serum trough levels. I'm sorry. That should be blood trough levels.

The topical exposure is intermittent in nature. The levels are for most patients only sporadically above the limit of quantification, but it is unknown at the present time whether tacrolimus levels at or near the application site are higher than systemic levels.

It is not inconceivable that if we were to be able to assay tacrolimus levels in lymph nodes that are draining the treated area skin or in the interstitial fluid immediately under these treated areas, that the tacrolimus levels might be higher than what we've observed in looking at whole blood.

Next slide.

So unresolved issues then. The minimum systemic exposure at which there is clinically

relevant tacrolimus ointment induced immunosuppression is unknown, and the possibility of regional immunosuppression induced by topical application with tacrolimus cannot be excluded.

Next slide.

In evaluating the .03 percent versus the .1 percent ointment, looking at the .03 percent, the advantages are that you may have fewer patients with detectable blood levels, and most patients with detectable blood levels seem to have lower levels.

The disadvantages are that it may have inferior efficacy compared to the 0.1 percent ointment, and it may be more associated with transient elevations above five nanograms per mL early in treatment.

Next slide.

Looking at the .1 percent ointment, the advantages of the .1 percent ointment compared to the .03 is that it may have superior efficacy, and there's no evidence of an adverse event signal suggesting greater toxicity with the .1 percent compared to the .03 percent ointment.

The disadvantage is that most of the patients treated with the .1 percent ointment who had detectable blood levels seem to have higher levels than what's seen with the .03 percent ointment.

And that concludes my talk.

ACTING CHAIRMAN STERN: Thank you very much, Dr. Okun. I'd like to thank you especially for showing us that the issue of safety of .03 versus .1 is even more complex when you look at what happens over time in these individuals, and it was very helpful to me.

I'm open for questions. Dr. Bigby.

DR. BIGBY: I just want to ask two questions.

I'd also like to invite Dr. Lawrence to respond if he so chooses.

The first one is: what is the total number of patients who were actually exposed to tacrolimus for more than a year in the material that you were given?

DR. OKUN: In other words, adults plus pediatric patients?

DR. BIGBY: Yeah, yeah, yeah.

DR. OKUN: Please give me a few minutes.

DR. BIGBY: Yes, sir.

DR. LAWRENCE: I may be able to help you also, Dr. Okun.

DR. OKUN: Okay.

DR. LAWRENCE: And believe me, I know what it's like to go through those slides.

(Laughter.)

DR. LAWRENCE: In the concentration of .1 percent, Dr. Bigby, 676 patients total.

DR. BIGBY: For the full one year?

DR. LAWRENCE: Yeah, greater than 12 months treatment duration. I have it broken down at greater than six months. It's 971.

DR. BIGBY: And then -- 600 and what?

DR. LAWRENCE: Six hundred and seventy-six at 12 months and greater and 971 at six months or greater.

ACTING CHAIRMAN STERN: That's duration from onset of therapy, but didn't you say that there were about 230, 240 days per year of actual treatment

use?

DR. LAWRENCE: These are patients that were on the study and then followed for the --

ACTING CHAIRMAN STERN: Right, right.

DR. LAWRENCE: But on average, yes, the number of days, treatment days, was about 279 days.

ACTING CHAIRMAN STERN: Oh, sorry.

DR. LAWRENCE: Yeah. This is very confusing. I apologize.

DR. OKUN: You know, I agree with Dr. Lawrence. I'm not sure I can give you a precise number because several of these patients obviously discontinued during the course of treatment. Several of these patients used treatment intermittently.

I would say roughly looking across all concentrations, adults and pediatrics, about 1,000 patients in the adults and about 1,000 patients in the pediatrics, and that includes folks exposed to .03, .1, and .3 percent. A total of about 2,000.

DR. LAWRENCE: Yeah, I was going to say the difference isn't clear. He's also capturing some of those patients in the .03, which I'm not telling

you, and I didn't include the .3 at all because we're not pursuing that one.

But I apologize. Certainly you are correct. There were even closer to 2,000 total exposed.

DR. BIGBY: Okay. Then the other question is what difference between vehicle and control was the original study powered to detect.

DR. LAWRENCE: Let me ask Mr. Satoi to answer that because I truly don't remember the difference between vehicle and the active treatment arms.

DR. SATOI: Original protocol have stated to detect (unintelligible) difference between vehicle and active group for the calculation of statistical power.

DR. TANG: You'll notice that your success rate ranges from the treatment group to the vehicle group, ranges from 20 to 30 percent. Also the discontinuation rate in the vehicle group is 40 percent higher than the treatment group.

I wondered have you done a sensitivity

analysis, a robustness analysis to see how your analysis can adjust for the patients who are actually on therapy, the duration of the patients who were on therapy.

DR. LAWRENCE: Again, I'll ask Mr. Satoi. I have a very quick tendency to defer --

DR. TANG: Yeah, this way though it will support your study.

DR. SATOI: I'm sorry. Could you repeat your question, please?

DR. TANG: In the vehicle group, the 64 percent of the patients discontinued. Have you done a secondary analysis to adjust for that? Would significant results still hold or the significance would be somehow attenuated?

DR. SATOI: Slide 892, please.

Actually for the primary analysis, as Dr. Lawrence mentioned, the last observation carried forward measure was used for the success analysis

DR. TANG: Yes, but by the time the patients were being treated is shorter on the vehicle. If the patients were, you know, persevering, you know,

for those with the (unintelligible) mouse you may have a little bit different result.

DR. SATOI: This slide shows we did some additional analysis to confirm the primary result, and this slide shows that one of those results, the success for three double blind studies using patient on treatment at least 21 days. It means three weeks.

So even using this criteria, we can see clear different between vehicle and true consideration for each studies, and also, this one is similar analysis using patient on treatment at least six weeks. So you can see still clear difference between the grand active groups.

So from those confirmatory analyses, we could conclude that the result of primary analysis is very robust.

DR. TANG: Okay. So, therefore, there is a consistent 20 to 30 percent difference throughout the treatment course.

DR. LAWRENCE: Yes, that is correct. Thank you.

ACTING CHAIRMAN STERN: Other questions?

Michael.

DR. BIGBY: This one is, again, for Dr. Okun.

So, you know, the clinically significant detectable difference between tacrolimus and vehicle that was considered significant is 30 percent, and you made the statement that a ten percent difference between .03 and .1 percent would be clinically significant. Why?

DR. OKUN: I chose a ten percentage difference merely for illustrative purposes. The purpose of that slide was to point out, as you said, that the study would only be powered to about .18 to detect a ten percentage point difference.

Clearly, if you regard a difference lower than that as still clinically significant, and I would venture to say that there are a lot of patients who suffer from atopic dermatitis who would feel that, you know, a difference less than ten percentage points would be clinically significant; the power would decrease accordingly.

So even setting ten percentage points as

a minimal standard or as a high hurdle, it's clearly not powered to detect a difference like that. In short, it was picked somewhat arbitrarily.

ACTING CHAIRMAN STERN: Other questions from the panel?

I have a couple. One is, and I address this to Dr. Okun, I found -- two parts to this question -- one is I found your subgroup analysis where I think out of about 16 or 17 comparisons you did, basically all but two of them went in one way. So if you're just looking at it as a coin toss, it comes out quite significant in terms of it almost always came out better for the subgroups however you slides and diced them, which is another way of kind of looking at the differences that persist.

So I found that actually in some ways a more persuasive argument for higher efficacy.

The second is I think you made quite clearly the point that there seem to be fairly clear evidence, especially in more severe people, that you got better faster with the higher concentration. Has there been any thought either by the company or by the

FDA to, in fact, have a differentiation in terms of initial usage for more severe and limitations on the stronger?

Because I think we've heard throughout that it takes less in the long run in terms of absorption, but you may, in fact, have less total absorption if you can take that period of very bad, extensive atopic eczema and shorten it. Has there been any thought to those issues?

DR. WILKIN: I think that could well be captured in the committee's deliberation on Question 4, and essentially it's the notion that if you start with the higher concentration, you literally close the door to percutaneous penetration more rapidly.

ACTING CHAIRMAN STERN: You've said it much better than I did. Yes, that was my question.

And then I had an informational question. There was a fair amount of data on zoster and on eczema herpeticum, and I don't know what the background rates of especially either zoster in people under 17. One out of 800 cases in less than a year of exposure to me seems like a lot for kids under 17, and

you pointed out that there were, I think, nine cases that we don't know whether they had simple chicken pox or zoster.

So I didn't know whether you thought -- you seemed to indicate that you didn't think that was a lot, and I understand one case is never a lot in any sample, but what was your opinion about that? Are there any data?

And, similarly, and I'd look really more to Dr. Paller and others for experience about eczema herpeticum as baseline in this kind of population. Are there data? Does this seem like a lot or a little?

DR. LAWRENCE: Okay. If we could have slide 1348, please.

If we're working together, we want to make sure we're on the same page. I think that's important for us.

These are our calculations of these events, the pediatric and adult, again, the long-term trials, Dr. Stern, and you see here eczema herpeticum. As I said, it's actually .8 percent, one percent;

adults, two percent.

The literature suggests a rate of about six percent, and, again, in zoster, three percent; again, chicken pox, less than one percent of adults, and the literature suggests about seven percent.

I will say the zoster literature, I believe, is a pediatric study for the zoster.

ACTING CHAIRMAN STERN: When you say incidence, you're saying that's seven cases per 100-person years? Is that what you mean by percentage?

I mean, to me incidence has to have a numerator and a denominator usually spoken as person-years or some other time. So are these all standardized by time of exposure or --

DR. LAWRENCE: These are studies basically where the literature was looking at the frequency of these events in a particular clinic experience, for example.

ACTING CHAIRMAN STERN: Yeah. So they may not have been standardized to time of exposure and may not be comparable.

DR. OKUN: If I may follow up on that, you

know, I suspect that any estimate of the baseline incidence of this is going to be quite variable from study to study, and your intimation that I was reasonably comfortable with, the rate that appeared for the definite herpes zoster, it was based on a recent article by Hope-Simpson which described a baseline incidence of about .74 cases per 1,000 per year in normal population.

We don't have any information that speaks to the baseline incidence in patients with moderate or severe atopic dermatitis, who quite conceivably could have a different baseline.

ACTING CHAIRMAN STERN: But is that a study of all herpes zoster in children? Because --

DR. OKUN: Yeah. That's in children.

ACTING CHAIRMAN STERN: In children. Really? Okay. Thank you.

DR. LAWRENCE: Would it be helpful to have Dr. Paller comment on that?

Okay. Thank you.

ACTING CHAIRMAN STERN: Any other questions on the part of the panel before we go to the

questions?

(No response.)

ACTING CHAIRMAN STERN: Dr. Wilkin, would you like to formally -- might it be sensible to go through and do one question at a time, or would that be the best way?

DR. WILKIN: And actually, you know, I went through the questions; you went through the questions. The sponsor at the beginning of their presentation went through the questions, and at the end of the presentation, they went through the questions.

(Laughter.)

DR. WILKIN: And so if repetition is the mother of learning, we all know the questions. So I'm not sure at this stage whether I need to read them to you.

ACTING CHAIRMAN STERN: Well, I think the first question perhaps. Is there any discussion about the first question, which is is there sufficient evidence for effectiveness of Protopic -- thank you for using that phrase -- .03 percent in the treatment

of atopic dermatitis?

Any questions about that? I think that's pretty much a slam dunk, as is sometimes said.

And do we hear a motion for a committee vote on, I guess, that, that there is sufficient evidence for the effectiveness of .03 percent protopic in the treatment of atopic dermatitis? Would someone like to move that?

DR. LIM: So moved.

ACTING CHAIRMAN STERN: Second?

DR. TANG: Second.

ACTING CHAIRMAN STERN: All those in favor on the committee who believe that to be the case?

(Show of hands.)

ACTING CHAIRMAN STERN: I take that that's everyone.

Okay. Now I think we come to data that when I read the materials before the meeting I thought was pretty straightforward, and now I think is more complicated, and perhaps we should come into some other parameters and perhaps if there's ambiguity about this as a total question, perhaps we might move

it as something else in Question 4 when we're talking about different durations of therapy.

So the second question: is there sufficient evidence for superior effectiveness of Protopic .1 percent compared to .03 percent, first in adults, then in children?

Comments?

DR. BIGBY: I would say the answer to that is definitely not in both groups of people. I mean, I think the thing you have to decide is how much of a difference is important.

ACTING CHAIRMAN STERN: I'm sorry. I misunderstood. You think there's evidence in both groups of people?

DR. BIGBY: That there is no difference.

ACTING CHAIRMAN STERN: There is no difference.

DR. BIGBY: Yeah. I mean so how much is a clinically important difference, I think, is the major issue to raise.

ACTING CHAIRMAN STERN: Okay. And?

DR. BIGBY: The data presented in adults,

I mean, I don't think that they want to make an argument about children. I mean, I think their conclusion about children is correct that there isn't any difference.

The magnitude of the difference that was demonstrated in adults was somewhere between five percent and ten percent. So if it's five percent, that means you have to treat 20 extra patients with .1 percent versus .03 to get one additional greater than 90 percent cure.

And then I think the largest difference demonstrated was nine, which means you have to treat about 11 patients. I mean, is that a significant difference? I mean, does that make it worthwhile?

And then the other part to that equation is what does -- is there an added risk difference in terms of .03 and .1 percent treatment?

ACTING CHAIRMAN STERN: I think those are exactly the -- the second part combined with the first are exactly the issues.

Other comments by the committee about whether or not there's a feeling that .1 in either

adults and/or children is superior to .03 in terms of efficacy, that the evidence supports that?

DR. ABEL: Well, one point was made that if you start with .1 and they have rapid improvement that first week, then there is going to be -- and then, say, switch to the .03 or the .3, then perhaps that there would be less toxicity or less absorption, and the atopic dermatitis would be improved. So there's less body area being treated, and you might be able to switch to the lower concentration.

ACTING CHAIRMAN STERN: I think that's inherently appealing, but the data to support that are extraordinarily limited. Having put forward that hypothesis, I should say that's wishing as hoping as opposed to data based.

But I think we should probably at this point really think about what the data support and then think about the inferences in clinical judgment when we get down the line.

So does anyone want to discuss Question 2 any further? Any other comments?

Do I hear a motion that there is or is not

sufficient evidence for superior effectiveness of .1 to .03 percent in adults?

DR. MINDEL: I'd like to make a motion that we not make a motion, that we just vote. This isn't parliamentary.

ACTING CHAIRMAN STERN: Okay.

DR. MINDEL: Is that all right? Just we'll have a vote.

DR. ABEL: What is "significant"?

ACTING CHAIRMAN STERN: Well, I think "significant" we're now using in a statistical sense, that we believe there's robust data that says, yes, this stuff in this group of patients as broadly defined, that there's good evidence that it's better than the other stuff at a lower concentration. That's how I'm taking significant as opposed to substantial or clinically important or whatever. I'm taking it in a formal definition.

How do other people feel about seeing that we're not going to address that directly; it's not key for us to vote on it and to go on?

DR. LIM: I guess my question on this is

that I think Mike did mention that the data is not probably as strong as it could be, but there are some differences. The question is what is the level of difference that we would consider to be significant.

What is the implication of these? You know, are you looking from the FDA point of view for us to say one way or the other so that only one strength would be approved or it would be both strengths?

Because I'm looking maybe just a few steps ahead down the road. If, indeed, there is a result of this discussion and our saying one way or the other would limit the availability of the concentration that is in the market, that may be potentially a disservice to some patients.

So I'm not quite clear what would the implication be on this part of the discussion.

DR. WILKIN: Well, the answer to Dr. Lim's question is yes, but --

(Laughter.)

DR. WILKIN: -- a longer explanation for the yes is that we really are interested not so much

in the safety element at this point. We're interested in is your sense -- and this is bringing, you know, science and clinical values, and you've heard the data set. Do you believe there is a superior effectiveness with the 0.1? Is there an effectiveness advantage to the 0.1 percent?

We're not defining for you what clinical significance would be. We're asking you to -- you've seen the data. We're asking you for your assessment of that.

ACTING CHAIRMAN STERN: My own opinion is that the weight of the evidence in adults is that if you look at all of the different parameters and you weight them, the various ways you can look at data, that the .1 wins often enough that even though it only makes it for one subgroup individually, that I think it is probably significantly more effective when you look at time to improvement, when you look at the number of subgroups where there is on a binary level superiority among adults. I think it is much more likely than not that it is significantly more effective according to the endpoints that were used in

the analysis, 90 percent or more clearing.

I don't think that the data to me in children is as persuasive as making me feel that there is sufficient evidence at this point. It doesn't mean it's not the case, but maybe they do want us to vote on that.

Because I think part of all of this is really what do we think we know, and what might there be additional information to formally address it before you might want to have the product labeled in that way. So I think this is really somewhat -- if I understood you, it's kind of information gathering. What are we comfortable with? Yes, we have enough data to answer this question, and we're really quite comfortable about it, or, no; maybe yes, maybe not, but we're not comfortable with the amount of information and telling you, yeah, we think it's almost certainly this way or the other way.

Is that correct?

DR. WILKIN: Yes. I mean, in essence, the art of any science, and that would include dermatologic clinical pharmacology is to try to get

the right answer with imperfect data, and saying imperfect data is not -- I'm not saying anything negative about what the sponsor has done.

(Laughter.)

DR. WILKIN: It's that all data coming from biological type experiments are imperfect to one extent or another.

DR. BIGBY: Please, just a point of clarification. What is the meaning of the vote? I mean, you know, so you vote. It's like majority rule, and who is actually eligible to vote?

ACTING CHAIRMAN STERN: That's a good point because I'm not sure you're eligible, Michael.

(Laughter.)

ACTING CHAIRMAN STERN: But we could get a clarification.

In fact, I know you're not eligible, and I'm sorry, but I think in the past at these hearings there's often differences of opinion, and really what we're looking for is not as any legal body, but an opinion body, and it's a stronger opinion if everybody on the panel believes something to be the case than if

it's divided.

So it's just a matter of sort of putting weight to the opinion, if not how do you say what the opinion of the panel is since there's in many issues a diversity and you'll never come to closure if it had to be unanimous on every vote.

So it really has absolutely, as I understand it, absolutely no regulatory or other things. It's sort of are we shouting with one voice or are there people shouting with very different voices, and it's just a way of getting on in the process.

So it really doesn't mean much if that's what you're worried about in terms of --

(Laughter.)

ACTING CHAIRMAN STERN: I'm joking. I'm joking. I know you're going to say that's not the case.

DR. WILKIN: Okay. That's not the case.

As it turns out, we really do like the vote at the end because it gives sort of a crisp summary to everything, but I would assure you that my

colleagues and I, and they're behind me; they can definitely attest to this; that we don't just look at how the votes went at the end of the meeting, you know, eight to two or that sort of thing. We rigorously go over the transcripts, and we spend hours looking at all of the comments and the thinking that goes into this.

And you know, you are our advisors, consultants. Industry can hire their own, talk to them away from an open setting, but this is the only way we get to talk to consultants, experts, and so we rely a lot on the discussion part for insights and things that that, you know, you pick out with the data.

ACTING CHAIRMAN STERN: With that said, I'd like to make one comment independent of whatever the outcome of these votes are, that I guess I would like to introduce one third thing, is it would be very interesting to me at least to have some data about the relative absorption safety profiles of short course of higher concentration followed by lower concentration versus lower concentration only, to see if there's a